and prevents the establishment of the expected coupling with cell 5. On the other hand, a pair of cells 5 in the same culture do become electrically coupled[6]. Thus, cell 5 is capable of establishing electrical coupling in the presence of 10^{-6} M serotonin, whereas cell 19 is not.

Clearly the importance of these findings depends upon the specificity of the chemotrope's action. Selectivity of cellular response has already been demonstrated, with cells 19 responding to serotonin at concentrations of 10^{-7} M and cells 5 not responding at all to concentrations up to 500-fold greater (5×10^{-5} M). Do other neurotransmitters have a similar action? If so, do they affect the same neurones; or is the growth of different neurone classes coded to respond to different neurotransmitters? Answers to these questions are needed before such intriguing observations can be said to reveal an action that is specific to either a class of cell or a type of neurotransmitter.

But is serotonin really involved in neuronal development? Although the authors are curiously silent on this point, further light can be shed on the unwritten significance of their findings. On either side of the brain in various gastropod molluscs is a large, unique neurone which projects to the buccal ganglion and often contains serotonin. In *Helisoma*, this cell is known as C1 (ref. 9); its axon and terminals are the only structures in the buccal ganglion that react with antibody to serotonin (unpublished observations cited in ref. 10). Electrical stimulation of C1 can initiate the buccal ganglion-generated feeding rhythm, an action that is mimicked by application of serotonin at 5×10^{-7} M to the whole ganglion[9]. Granzow and Kater[9] have taken this to imply that serotonin is the putative neurotransmitter of C1. Two pieces of unpublished evidence (J. Goldberg and S.B. Kater, personal communication) suggest that this cell similarly is a source of serotonin during embryonic development. Firstly, the cytotoxic transmitter analogue 5,7-dihydroxytryptamine, which acts selectively on serotoninergic neurones, temporarily depletes serotonin when applied to embryos. If it is used at a stage when cell 19 is extending neurites, changes in the morphology of the adult cells 19 result, suggesting that these cells in the embryo respond to the same signals *in vivo* as do their adult counterparts *in vitro*. Secondly, immunocytochemical staining indicates that C1 is present and charged with transmitter at this same embryonic stage, indicating the possibility that C1 is the source of serotonin. If C1 is charged with serotonin at a time in embryonic development when the growth of cell 19 neurites is sensitive to it, all that remains to be demonstrated is that serotonin is actually released at both the time and the concentration necessary to achieve the desired morphogenetic effect. This is a tall order, but whoever fills it will write a new chapter in neural development. □

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Geophysics

Global sea level trends

From J.E. Hansen

GLOBAL sea level is rising but at a rate, of about 1-2 mm per year or 10-20 cm per century, that is difficult to measure accurately. Several mechanisms may contribute to the net increase but it is difficult to distinguish their individual contributions. These conclusions are emphasized by Barnett[1] and in several other recently published papers.

Sea level trends are estimated from records of tide gauge stations, which are spread very inhomogeneously around global shorelines. The trends recorded at different stations range widely from an increase in sea level of one metre per century in Louisiana to a fall of one metre per century in parts of Scandinavia. The largest trends result from vertical shoreline movements (caused by river delta sedimentation in Louisiana and post-glacial crustal uplift in Scandinavia), but many factors introduce local variability, including changes of ocean currents, ocean heat content, atmospheric pressure, atmospheric wind patterns, local vulcanism and tectonism.

Some of the local factors are unimportant when averaged over a period of several decades; others can be identified at individual recording stations, data from which can then be excluded from global analyses. Even so, Barnett stresses that the global estimate he obtains is still uncertain by at least 50 per cent, because variations of that size emerge from different ways of averaging over the globe. Barnett's principal result — a 14 cm rise in global sea level in the past century and a rate of 23 cm per century in the past 50 years — is consistent with the results of previous investigators. This is not surprising because, as Barnett notes, most investigators have worked with essentially the same data set.

Trends in sea level have practical significance. The current rise of approximately 30 cm per century along much of the US east coast, which is still subsiding be cause of the flow of material in the Earth's mantle towards the Hudson Bay region of post-glacial rebound, leads shoreline geologists and engineers to recommend against a strategy of installing stabilization structures to arrest the erosion of beaches. The rising sea level, combined with natural shoreline fluctuations and often with erosion caused by the 'stabilization' structures, is making it essential for coastal planners to take into account a shifting and generally retreating shoreline. Present sea level trends have an even more dramatic effect in Louisiana, where a single county (Terrebonne Parish) is losing 20 km^2 (6,000 acres) of land per year to the encroaching sea.

But the main reason for the growing interest in sea level[2,3] is the concern that global warming, due to increasing atmospheric CO_2 and trace gases, may lead to partial disintegration of the polar ice sheets and a subsequent large increase in the rate of rise in sea level. If entirely melted, the West Antarctic ice sheet, thought to be the most vulnerable since it rests on bedrock well below sea level, would raise global sea level by about 6 m. Greenland contains a similar amount of ice and East Antarctica has an order of magnitude more. Glaciologists estimate that West Antarctica could conceivably disintegrate in a time as brief as 200–500 years[2-4]. Even without any net melting from the other ice sheets, such a fast response would have enormous practical impact, with the sea level on almost all coastlines rising at a mean rate of one metre or more per century.

Does the current increase in global sea level of 10-20 cm per century mean that the ice sheets have aready begun to disintegrate? No. First of all, part of the rise probably results from the continuing influence of post-glacial isostatic disequilibrium[5,6], the high viscosity of the Earth's mantle implying that coastline elevations are still adjusting to the shift of water mass from continent to ocean which occurred with the melting of Würm-Wisconsin ice in the Northern Hemisphere. Models for crustal deformation[6] suggest that this could account for a rise of 2-5 cm per century.

Thus, of the nominal 14 cm rise in sea level per century reported by Barnett[1], only about 10 cm is due to an increase in ocean water volume. Gornitz *et al.*[7] estimate that a rise of 3-6 cm may be due to thermal expansion of ocean water in response to the 0·5°C global surface warming of the past century[8]. This warming is probably also responsible for the mean retreat of mountain glaciers in the past century, which Meier[9] estimates to contribute an additional rise in sea level of 2-5 cm.

In view of the large recorded variations in sea level rises and in view of several other processes (such as ground water discharge and dam construction) which could account for changes in ocean water volume of 1-3

cm per century, we can conclude only that polar ice sheets must have been in approximate mass balance (±10 cm of sea level) during the past century. This conclusion does not reduce the importance of understanding the mass balance of ice sheets, which is essential if we are to anticipate the effects of sea level of the 'greenhouse' warming predicated for coming decades. The fact that thermal expansion of ocean water and the retreat of mountain glaciers contributes significantly to sea level rise will make any future disintegration of ice sheets all the more important.

The task of analysing sea level and its relation to climate trends is a good example of an emerging class of 'global habitability' problems that many scientists expect to become increasingly important as man's impact on the global environment continues to grow. The scientific challenge is to develop a quantitative understanding of environmental changes. This requires us first to distinguish long-term trends, both man-made and natural, from short-term fluctuations. To meet this challenge will require the definition, implementation and maintenance of observation programmes on the time scale of decades.

Progress in understanding the relation between sea level and climate will depend especially on accurate monitoring of the volume of the major ice sheets. This could be achieved with precise satellite altimetry using existing technology[10,11], the chief requirement being a polar-orbiting platform. Measurement of the thermal expansion of ocean water will require repeated hydrographic sections of the major ocean basins, necessitating regular cruises to monitor the ocean's temperatures, density and salinity structure. It should also be possible to determine net sea-level trends more accurately by means of additional well-chosen tide stations, mainly in the Southern Hemisphere. □

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Neurobiology

Molecular tinkerings that tailor the acetylcholine receptor

from Charles F. Stevens

ON PAGE 364 of this issue, the Kyoto laboratory of S. Numa reports another dramatic contribution to understanding the molecular basis of neurotransmission. By the technique of site-directed mutagenesis (which I have briefly explained in *Trends in Neurosciences*. **7**, 306; 1984), Mashina *et al.* have made deliberate alterations in the structure of one of the subunits of the acetylcholine receptor (AChR) to test the functions of its parts. As usual, Numa's laboratory has done it grandly: two and a half dozen deletions and substitutions have been made and their effects analyzed.

First, some background. The AChR is one of several integral membrane proteins that are responsible for the electrical activity of the nervous system. Each of the proteins forms a channel that is selectively permeable to ions; the job of AChR is to transduce the signals delivered by acetylcholine (released from a presynaptic nerve terminal) into increased cation permeability of the postsynaptic membrane, in which the receptor molecules are embedded. The receptor is composed of four different membrane-spanning subunits (alpha, beta, gamma, and delta); a single AChR contains two copies of alpha, the subunit that binds acetylcholine, and one copy each of the others. Although each subunit type has a distinct amino acid sequence and is coded by a separate gene, they all share the basic structure that is illustrated for alpha in the bottom section of the figure. The amino-terminal half of the receptor is extracellular. The carboxy-terminal half, according to the models of Finer-Moore and Stroud (*Proc. natn. Acad. Sci. U.S.A.* **81**, 155; 1984) and Guy (*Biophys. J.* **45**, 249; 1984) passes five times across the membrane. Four of these membrane-spanning segments (denoted M1 to M4 in the figure) are hydrophobic, and one (MA) is amphipathic; that is, it has charged side chains of amino acids displayed along one face with the other faces being hydrophobic. Both models postulate that each of the five subunits contributes an amphipathic helix to form the charge-lined walls of a water-filled pore through which ions pass. The hydrophobic helices are packed around this pore to stabilize the structure.

The alpha subunit has a binding site for acetylcholine that Karlin's laboratory (Kao, P.N. *et al. J. biol. Chem.* **259**, 11662; 1984) has recently shown to be near a particular cysteine (C192) that participates in a disulphide bond with one of the other three cysteines in the extracellular portion of the protein. It also has a single site for N-glycosylation at asparagine 141 (N141).

For AChR to transduce the acetylcholine signal into the response of increased cation permeability, it employs three functions: acetylcholine binding, gating (that is, opening the door that covers the pore), and ion permeation and selectivity (that is, the flow of certain cations like sodium, but not anions, through the pore). These three functions are well studied physiologically, but it has not been known how they arise from the molecular structure of the receptor. The accomplishment of Mashina *et al.* is to provide, at least in a preliminary way, an assignment of these functions to specific regions of the alpha subunit of AChR. After site-directed mutagenesis, the altered alpha subunit cDNA was used to make a corresponding mRNA, which was injected into frog oocytes together with normal mRNAs for the other three subunit types. The injected oocytes synthesize and assemble AChR, which is inserted into the surface membrane of the oocyte where its function can be studied. For each alteration, some of which deleted regions of the alpha subunit and some of which substituted one amino acid for another, the total amount of modified AChR made by the oocyte was determined with antibodies. In addition, the function of the AChR was assessed by measuring both the binding of ligands specific to the acetylcholine binding site (α- bungarotoxin and carbamyl choline) and gating combined with permeation in terms of the current flow produced by acetylcholine application.

As illustrated in the figure, various deletions were made in each of the five postulated membrane-spanning regions and in the cytoplasmic region between MA and M4; furthermore, each of the five cysteines of the subunit was separately replaced by a serine, and aspartic acid was substituted for an asparagine (N141). Most of the results fall into one of three categories: no effect observed (N in the figure); binding still intact but no gating or permeation (P); neither binding nor permeation functions intact (B). In some instances, decreased quantities of protein are detected, probably because one or more subunits fail to fold and assemble. The antibody-detection methods used cannot distinguish between cytoplasmic subunits and those displayed on the cell surface. In general, the findings support the models published by Finer-Moore and Stroud and by Guy for the membrane-spanning portions (although there may be a difficulty interpreting one large MA deletion) and are consistent with the location of the acetylcholine-binding site near C192 as suggested by Kao *et al.* Particularly noteworthy is the observation that eliminating the N-glycosylation site at N141 seems to disrupt the assembly and possibly the function of the AChR. The profound effects of replacing any of the four extracellular cysteines by a serine are